GLOBAL SCIENCE LIBRARY

EDITORIAL

Diabetes Research and Metabolism

# Hypoxic-Hypercapnic Environment As A Model of Hypometabolism, Calorie Restriction, Hypoglycemia and Non-Medicamentous Treatment of Related Pathology

**Vadim E Fraifeld[1,2*] and Khachik K. Muradian[1*]**

*[1]State Institute of Gerontology of National Academy of Medical Sciences of Ukraine, Ukraine*
*[2]The Shraga Segal Department of Microbiology, Immunology and Genetics, Center for Multidisciplinary Research on Aging, Ben-Gurion University of the Negev, Israel*

Comparative analysis supports the idea that extreme longevity can be associated with hypometabolism provoked by hypoxic/hypercapnic lifestyle. Of particular interest is comparison of two closely related model organisms – the naked mole-rat (NMR) and mouse. NMR has around 4-fold lower metabolic rate and lives almost an order of magnitude longer than mouse. Most importantly, NMR preserves high physical and reproductive activity up to the very advanced ages and is exclusively resistant to hypoxia and spontaneous or induced forms of age-related pathology (heart attack, stroke, cancer, osteopenia, etc.). Colonies of NMR live in deep and poorly ventilated borrows, which results in an elevated $CO_2$ and reciprocally decreased $O_2$ in the breathing air. We hypothesized that such hypoxic-hypercapnic environment (HHE) could be a cause of the extraordinary longevity and disease-resistance of NMRs and wandered if the same kind of simple intervention could induce similar changes in mice [1].

HHE in our research was modeled by keeping mice in hermetically closed glass jars for 3 h (acute HHE) or in partially ventilated plastic cuvettes for 30-90 days (chronic HHE) [1]. In acute experiments, HHE exposure caused gradual elevation of $CO_2$ content and proportional decrease of $O_2$ and induced several-fold decrease in the gaseous exchange rate ($Vo_2$ and $Vco_2$). In chronic experiments, an around 40% decline in metabolic rate was accompanied by a comparable decrease in food and water consumption and provoked swift decrease in body weight, obviously because of utilization of the fat deposits. In both acute and chronic HHE, body surface temperature decreased by some 2-3 °C which corresponds to a 3-4 °C decrease in the body core temperature. To our best knowledge, HHE is the most powerful model of long-term hypometabolism and hypothermia and opens unprecedented opportunities for modification of biological processes. HHE could be regarded as a model of 'voluntary' calorie restriction because the experimental animals decreased food consumption by their own good will in an ad libitum feeding regime. Moreover, HHE might ameliorate negative effects of the overweight and metabolic syndrome. The described effects are most likely physiologically well-orchestrated, as it follows from decreased expression of the hypothalamic neuropeptide Y and agouti-related peptide which stimulate appetite, food intake and fat storage in normal conditions.

$O_2$ and $CO_2$ are the substrate and product of oxidative phosphorylation. However, they have most probably different targets and can alternate cooperation with competition. According to our working hypothesis, hypometabolic effects of hypercapnia are primarily associated with deceleration of the decarboxylation reactions occurring in mitoplasm and resulting in conversion of oxidized NAD into the reduced form (NAD- → NADH), whereas $O_2$ participates in oxidative phosphorylation only at the very end of the electron transport chain (ETC) by utilizing energy-exhausted electrons in a reaction: $4e^- + 4H^+ + O_2 = 2H_2O$. Thus, hypercapnia may provoke lesser generation of NADH whereas hypoxia can 'logjam' electron flow in the ETC. It is important to ensure proportionality between these two pathways by, so called, balanced HHE, as was in our experiments. Otherwise, it could result in accumulation of potentially dangerous high energy-carrying NADH, or jam ETC and provoke excessive generation of free radicals. Equal concentrations of $CO_2$ and $O_2$, however, do not ensure identical hypometabolic effects. In our experiments, augmenting the hypoxic effects by preliminary addition of 25% $N_2$, $H_2$, He or Ar did not significantly alter the dynamics of gaseous exchange (unpublished data; paper in preparation). In striking contrast, preliminary application of only 3% $CO_2$ sharply dropped the rate of oxidative processes, thus evidencing that inhibitory effects of hypercapnia could be stronger than hypoxia. Moreover, it is well known that hypoxic effects are regulated mostly by HIF-1 which expression and protein synthesis are dramatically increased in hypoxia [2]. In contrast, hypercapnia apparently has the opposite effects. It surprisingly suppresses HIF-1 expression and accelerates the HIF-1 protein degradation [3]. In our chronic experiments, HHE also induced almost a two-fold decrease in HIF-1α expression throughout the whole period of exposure, thus clearly demonstrating that effects of hypercapnia dominate over the effects of hypoxia. From this point of view, it seems relevant mentioning that the most intensively studied experimental models and clinical cases of hypoxia are usually associated with tissue ischemia or hemorrhage (stroke, heart attack etc). In such situations $O_2$ supply is often decreased below the level of a cell survival. However, the decreased blood flow and $O_2$ delivery almost always means a proportional decrease in $CO_2$ outflow, thus indicating that stroke or infarction are rather typical cases of HHE. Therefore, in such situations it seems reasonable to focus primarily on minimizing negative consequences of the dominating hypercapnic effects than hypoxia.

The decreased rates of oxidative phosphorylation in HHE could be compensated by activation of glycolysis. In our experiments, it was proved by an increased concentration of lactate in the brain. Because of the lower efficiency of glycolytic energy generation, HHE could facilitate glucose utilization with a concomitant decrease of the blood sugar content. We observed around one-third decrease of the blood glucose content in HHE-adapted

mice. In cooperation with the lesser food consumption and leaner body composition, it could result in amelioration of negative consequences of the metabolic syndrome and primarily diabetes. In experiments with streptozotocin model of diabetes, the idea was supported by insignificant changes of blood glucose in mice kept in HHE, in contrast to several fold increase of blood glucose in streptozotocin-treated animals kept in normoxic conditions (unpublished data; paper in preparation).

It is known that NMRs are highly resistant to cancer development. Maintenance of mice in HHE also resulted in a 2-3- fold decrease in the growth of Lewis lung carcinoma. Moreover, while in normal atmosphere, all the mice injected with carcinoma cells developed tumors and died, some animals kept in HHE did not develop carcinomas at all or, surprisingly, showed retrograde tumor development, when already registered sizeable carcinomas gradually shrunk and disappeared (unpublished data; paper in preparation). We believe that study of HHE effects on other types of neoplasia is a highly promising area of research. It could also be applied in treatment of many other conditions, wound healing included. Wound healing occurs usually quicker in animals with higher metabolic rate, and we expected a slower wound recovery in HHE. However, significant acceleration was observed in skin wound healing in HHE-exposed mice which could be attributed to enhanced cell proliferation or activation of mesenchymal stem cells [1].

The proposed model of HHE is simple, reliable and self-produced, i.e. it does not require usage of complex technical equipments and sophisticated gadgets. It could have wide application in areas ranging from treatment of various pathologies to decreasing O2 and food requirements in conditions of limited resources. The latter is practically inevitable in deep space travelling and upcoming colonization of planets. Every saved percent of $O_2$ or dietary calorie could be a critical issue in such situations, and the proposed optimization of metabolic costs can be 'a simple solution of complex problems'. It is also worth mentioning that life originated and most part of evolution occurred in conditions of severe hypoxia and hypercapnia [4]. Taking into account the notorious conservatism of the basic life-supporting systems, it is tempting to speculate that 'deep inside' all biological systems are hypoxic/hypercapnic by their essence. In HHE conditions, at least some of the basic biological systems will feel like retuning home from a faraway voyage.

Summarizing, HHE might have not only positive but host of negative effects. However, it could easily be combined with other medicamentous and non-medicamentous methods of treatment. With this in mind, the main task here is to create specific conditions for maximizing the positive and minimizing negative effects of HHE. Such research is only initiated and could be recommended for further experimental exploration. Only future investigations will show whether HHE could find a real application in everyday life and clinical practice.

## References


1. Tolstun D, Knyazer A, Tushynska T, Dubiley T, Bezrukov V, et al. Metabolic remodeling of mice by hypoxic-hypercapnic environment: imitating the naked mole-rat. *Biogerontology.* 2020; 21: 143-153.
2. Semenza GL. Hypoxia-inducible factors in physiology and medicine. *Cell.* 2012; 148: 399-408.
3. Selfridge AC, Cavadas MA, Scholz CC, Campbell EL, Welch LC, et al. Hypercapnia Suppresses the HIF-dependent Adaptive Response to Hypoxia. *J Biol Chem.* 2016; 291: 11800–11808.
4. Catling DC, Zahnle KJ. The Archean atmosphere. *Sci Adv*. 2020; 6: eaax1420.



***Correspondence:** Vadim E. Fraifeld, The Shraga Segal Department of Microbiology, Immunology and Genetics, Center for Multidisciplinary Research on Aging, Ben-Gurion University of the Negev, POB 653, Beer Sheva 8410501, Israel, Tel: +972-8-6477292, Fax: +972-8-6477626, E-mail: vadim.fraifeld@gmail.com

Khachik K. Muradian, State Institute of Gerontology of National Academy of Medical Sciences of Ukraine, Ukraine, Tel: +38-093-0324074, Fax: +38-044-4329965, E-mail: muradian1944@gmail.com



**Rec**: 03 Jun 2021; **Acc**: 24 Jun 2021; **Pub**: 27 Jun 2021

Diabetes Res Metab. 2021;2(1):110
DOI: 10.36879/DRM.20.000110